

## REMARKS

This communication is submitted under the same cover as Applicants' CPA Request Transmittal. Applicants' September 6, 2000 amendments, submitted as part of their response to the final rejection of the claims, were not entered by the Examiner. Accordingly, the amendments herein are to the claims as they existed following Applicants' November 17, 1999 Amendment and Response (Paper No. 7).

Upon entry of the amendments herein, claims 1-6, 12 and 14-29 are pending in the application. Claims 1-6, 12 and 14 have been amended; claims 7, 8 and 13 have been canceled; and new claims 15-29 have been added. No new matter has been introduced by any of the amendments herein.

Independent claims 1 and 12 have been amended, without prejudice, to reflect only the embodiments of the invention having polymeric matrix formulations. As a result, the pending claims are no longer directed to embodiments of the invention having diffusion-controlled membrane coatings. In the wake of the amendment of claim 1, claims 7 and 8 have been canceled. In the wake of the amendment of claim 12, claim 13 has been canceled. Applicants have made these amendments only in the service of expediting prosecution of the present application and they maintain the right to resume prosecution of any withdrawn subject matter in a continuation application.

Claims 1 and 12 have also been amended to clarify that the claimed pharmaceutical compositions afford sustained release of

fluvastatin following ingestion. Support for this change is inherent in, and found throughout, the specification.

Claims 1 and 12 have further been amended to more clearly recite that the pharmaceutical composition comprises fluvastatin as an active ingredient and a polymeric matrix formulation comprising at least one polymeric matrix material. Support for claiming a matrix formulation comprising a single polymeric matrix material, as done in claims 15, 16 and 22, is found in the disclosure from page 7, line 21 to page 8, line 20 of the specification. Support for claiming a matrix formulation comprising more than one polymeric matrix material is found on page 8, line 22 of the specification. Support for claiming a matrix formulation consisting of precisely two matrix materials, as done in claim 21, is found in the examples.

New claims 17-20 are directed to compositions comprising specific classes of polymeric matrix material constituents. Support for claims 17-20 is found in the disclosure from page 7, line 21 to page 8, line 22 of the specification as filed.

New claim 23 and its dependent method claims, 24-28, are directed to a method for obtaining sustained release of fluvastatin following ingestion without the use of large amounts of slow-release excipients and/or osmotic pressure-controlled formulations. New claim 29 is directed to a pharmaceutical preparation prepared according to the method of claim 23. Support for new claims 23-29 is found, e.g., on page 6, lines 1-13 of the specification as filed, along with the disclosure on

pages 7-10 of the specification and Examples 1-3 which appear on pages 10-13 of the specification.

The final rejection of claims 1, 2, 5, 6 and 12-14 for allegedly being unpatentable under 35 U.S.C. §103(a) in view of U.S. Patent No. 5,462,749 to Rencher ("Rencher") was maintained in the parent application. The Examiner is on record as believing that the Rencher teaching of the requirement of xanthan gum as a component, the general Rencher teaching that "water insoluble vehicle materials will retard release" of actives, and the general Rencher inclusion of cholesterol-lowering agents among the actives constitute a bar to patentability of the instant invention.

In the first place, Applicants reiterate something the Examiner apparently has not appreciated: Rencher uses xanthan gum in combination with sodium carboxymethylcellulose to confer bioadhesive properties to the formulations; one of skill in the art would recognize this. Furthermore, even if Rencher is concerned with sustained release, it is certainly not at all in connection with formulations having sustained release following ingestion.

Rencher is directed to drug-release formulations applied to the site of action, not those which are swallowed (ingested) so as to allow drug absorption via the gastrointestinal tract of a patient. Support for this assertion is found in Rencher, col. 4, lines 22- 28 where it is disclosed that the preferred dosage forms are "administered orally, nasally, rectally, vaginally, ophthalmically, optically, or topically." It is apparent from

col. 4, lines 26-28, that the intended meaning of "orally" as used in line 23 refers to the topical application of the bioadhesive gel of Rencher to the site of action in the mouth. The totality of the teaching of Rencher is directed to bioadhesive pharmaceutical carriers which release a pharmaceutical at the site of action and the problems solved thereby in the treatment of moist membranes of the body. (See Rencher, col. 1, lines 17-30 and 49-53.)

In contrast, the present invention is directed to controlled-release pharmaceutical preparations of fluvastatin which are ingested, so that fluvastatin is absorbed by the gastrointestinal tract into the bloodstream, and, like other HMG-CoA reductase inhibitors, acts in the liver to reduce the level of circulating LDL cholesterol. The bioadhesive quality of the formulations of Rencher which makes the drug carried therein remain at a moist area of application, such as the mouth, is contradictory to the purpose of obtaining a controlled-release ingested formulation of a drug.

Further, while, as the Examiner correctly asserts, Rencher cites, at col 3., line 44, cholesterol-lowering agents as one drug class which can be included in the bioadhesive dosage form, no support is found in Rencher for a controlled-release ingested formulation of any cholesterol-lowering agent. Moreover, since the stated object of Rencher is to provide bioadhesive drug formulations applied to the site of action, the inclusion of cholesterol-lowering agents among the diverse list of pharmaceutical actives which can be included in the bioadhesive

dosage form is unsupported, since, as stated, the site of action of fluvastatin and all HMG-CoA reductase inhibitors is in the liver, an internal organ.

Thus, the "controlled release" of the Rencher semisolid or solid, topical formulation and such release with respect to the ingested instant formulations are not at all the same. The issue raised by the Examiner of the Rencher recitation of the "highly soluble drug" boric acid as an active is thus not of relevance to the consideration of patentability of the instant invention. Applicants note further that the ingestion of boric acid, the Rencher active cited by the Examiner, is, to say the least, contraindicated. Applicants have argued, rightly, that they have addressed the problem, ignored by Rencher (and the other cited prior art), of delivering by ingestion a highly soluble substance in a sustained-release vehicle.

Applicants note still further that the Rencher examples have benzocaine as the active ingredient; the Rencher definition of what constitutes a "highly water soluble drug" is not that understood in the field. Benzocaine has an aqueous solubility of 1g/2500ml (Merck Index, 11<sup>th</sup> Ed., p. 1114, copy provided with Applicants' previous response); fluvastatin has a solubility of more than 50g/1000ml (instant specification, p. 5, ll. 7 and 8). The instant specification defines "water-soluble" as a solubility of more than 30g/1000ml at body temperature (p. 7, ll. 6 and 7).

In the September 25, 2000 Advisory Action in the parent application (Paper No. 11), the Examiner gave as a reason for maintaining the final rejection: "with regard to Rencher,

intended uses are not patentable limitations and prior art is presumed operable (MPEP 2121)."

In the first place, Applicants have not argued that the Rencher invention is inoperable per se. On October 23, 2000, Applicants' agent discussed this issue, inter alia, with the Examiner. The Examiner explained that what prompted his understanding that Applicants were questioning operability were Applicants' September 6, 2000 remarks (reiterated hereinabove) regarding the incompatibility of using fluvastatin, the active agent of the instant invention, and the goal of Rencher to apply a formulation directly to the site of action. However, as clarified by Applicants' agent in the discussion, said arguments cannot be construed as an attempt to cast doubt on the operability of the Rencher invention; rather Applicants' remarks were one facet of their argument that one of skill in the art would not be led to, or motivated to try, the instant invention in light of the Rencher disclosure (or, for that matter, any other knowledge in the field at the time).

Furthermore, the Examiner's implication that the instant invention merely constitutes a new use of an old product is inappropriate. Applicants note that the rejection in view of Rencher is one of obviousness, not of anticipation. Thus the Examiner himself has acknowledged that the instant compositions are not literally taught by Rencher, and the "intended use" argument does not carry weight in the present assessment of patentability.

For all the reasons set forth above, the present invention is not obvious in view of Rencher. Withdrawal of the claim rejections in view of Rencher is requested.

The final rejection of claims 1-4, and 12-14 under 35 U.S.C §103(a) for allegedly being unpatentable over U.S. 5,576,016 to Amselem et al. ("Amselem") or U.S. Patent 5,023,089 to Sakamoto et al. ("Sakamoto") was also maintained in the parent application. The Examiner is on record as believing that it would have been obvious to one skilled in the art to deliver the fluvastatin of the instant invention using the vehicle of Amselem or Sakamoto.

In the first place, the vehicles of Amselem and Sakamoto cannot, as the Examiner supposes, be considered as "solid matrices." The Examiner made this assessment in Paper No. 11 but provided no support therefor.

The vehicle of Amselem is an entirely different drug delivery formulation than that of the present invention. Amselem teaches a pharmaceutical composition comprising nanoemulsions of particles comprising a lipid core, composed of lipid, which may be a wax, stabilized by at least one phospholipid envelope. (See col. 2, lines 29-33). The compositions of Amselem, as described therein, have features intermediate between liposomes and oil-in-water emulsions. In contrast, the present invention is not a nanoemulsion as described in Amselem, but a solid matrix. Matrix formulations according to the ordinary meaning in the art are those comprised of aggregated mixtures of granulate constituents optionally compressed together.

Further, the stabilizing phospholipid envelope(s) is an essential feature of the Amselem formulations; the present invention does not include such a feature. Therefore, the vehicle of Amselem and the matrix of the present invention are entirely different drug delivery systems. Inclusion of fluvastatin as active ingredient in the composition of Amselem cannot result in Applicants' invention.

Sakamoto teaches sustained-release preparations for water-soluble pharmaceuticals comprising two or more fats having different melting points wherein manufacture of the preparation comprises a first step of maintaining the temperature of the mixture or suspension of components above the melting point of the fat with a higher melting point, followed by spray cooling to form granules, and then an annealing step at a temperature between that of the lower-melting-point fat and the higher-melting-point fat. (See col. 1, lines 40-59.) The formulation of Sakamoto consists of a mixed melt of fats, and is therefore not a matrix according to the ordinary meaning in the art.

The present invention, as claimed, relates to matrix formulations of fluvastatin. Advantageously, the matrix formulations of the present invention may employ only one matrix material or a combination of matrix materials. Further of advantage, preparation of the formulations of the present invention does not require any melting or spray cooling technique.

The formulations according to Amselem and Sakamoto are not matrix formulations according the ordinary meaning in the field,

i.e., the meaning conveyed in the instant specification and claims. Matrix formulations according to the ordinary meaning are those comprised of aggregated mixtures of granulate constituents optionally compressed together.

The final rejection of claims 1, 2, 7, 8, and 12-14 under 35 U.S.C. §103(a) for allegedly being unpatentable over U.S. Patent No. 5,395,626 to Kotwal et al. ("Kotwal") or U.S. Patent No. 5,238,686 to Eichel et al. ("Eichel") was maintained in the parent application. It remains the Examiner's opinion that it would be obvious to deliver the fluvastatin of the instant invention using the vehicle of Kotwal or Eichel.

The basis for this rejection was the inclusion of diffusion-controlled membrane coated formulations among the possible components of the instant compositions. However, the claims pending in the present application as a result of this Amendment are no longer directed to diffusion-controlled membrane coated formulations of fluvastatin, but, instead, are only directed to polymeric matrix formulations. Therefore, as a result of the claim amendments made herein, the claim rejections in view of Kotwal and Eichel have been rendered moot.

Having said this, however, Applicants also wish to maintain, for the record, their stance that neither the teachings of Kotwal nor those of Eichel constitute a bar to patentability of the claims, even as they were prior to amendment herein. The amendments herein limiting the claims to polymeric matrix formulations have been made solely in the interest of focusing attention on a narrower range of sustained-release materials, and

any issues arising in connection therewith, and thus in the interest of streamlining prosecution of the present application.

Kotwal discloses a multi-layered, controlled-release pharmaceutical dosage form consisting of a drug-containing core and at least one other drug-containing layer, each surrounded by a controlled-release layer. Eichel discloses a dual-wall, coated dosage form for a water-soluble drug having an inner-wall microencapsular control coating and an outer-wall enteric coating (See col. 3, lines 22-25.) Neither of these references can be said to lead one to preparation of a composition comprising a water-soluble salt of fluvastatin and a diffusion-controlled membrane coated formulation.

Applicants have found, unexpectedly, that fluvastatin, a highly water-soluble drug by any accepted definition of the term in the art, is, despite its high solubility, released over a prolonged period of time when formulated according to the instant invention and subjected to conditions enhancing drug release. Even more unexpectedly, the release of fluvastatin from the claimed compositions is even slower than the release from similar compositions of test drugs with lower water solubility. (See, e.g., page 12, lines 15-19, referring to FIG. 2, of the specification as filed.) Nothing in the cited prior art provides any expectation or suggestion of these observed phenomena.

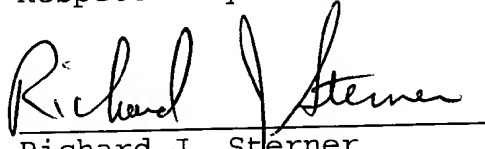
As set forth above, the instantly claimed subject matter is patentably distinct from the disclosure of the cited references. Furthermore, the amendments herein to the claims have put them into proper form for allowance. No new matter has been

introduced by said amendments. Reconsideration and allowance of pending claims 1-6, 12, and 14-29 are respectfully requested.

The Assistant Commissioner is hereby authorized to charge any fee which may be due for any reason to Deposit Account No. 23-1703.

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Respectfully submitted,

  
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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (twice amended) A pharmaceutical composition having [for] sustained release of fluvastatin following ingestion, said composition comprising a water-soluble salt of fluvastatin as active ingredient and a polymeric matrix formulation comprising at least one polymeric matrix material. [being selected from the group consisting of matrix formulations, diffusion-controlled membrane coated formulations and combinations thereof.]

2. (twice amended) The [A] pharmaceutical composition according to claim 1 wherein the water-soluble salt of fluvastatin is the sodium salt.

3. (amended) The [A] pharmaceutical composition according to claim 1 or 2, wherein the matrix formulation [which] is an eroding matrix formulation.

4. (twice amended) The [A] pharmaceutical composition according to claim 3 wherein the at least one matrix material [is selected from the group consisting of] comprises polyethylene oxide, hydroxypropyl methyl cellulose, [and] paraffin or a combination thereof.

5. (amended) The [A] pharmaceutical composition according to claim 1 or 2, wherein the matrix formulation [which] is a noneroding matrix formulation.

6. (twice amended) The [A] pharmaceutical composition according to claim 5 wherein the at least one matrix material comprises [is selected from the group consisting of] xanthan, [and] polyvinyl chloride or a combination thereof.

12. (twice amended) A method for the treatment of hypercholesterolemia comprising administering to a mammal a therapeutically effective amount of a pharmaceutical composition having [for] sustained release of fluvastatin following ingestion, the composition comprising a water-soluble salt of fluvastatin as active ingredient and a polymeric matrix formulation comprising at least one polymeric matrix material.

14. (amended) The method according to claim 12 [or 13], wherein the mammal is a human.